DETERMINING BASELINE PREVALENCE FOR PROVIDER-DIAGNOSED MULTIPLE SCLEROSIS (MS) AND AMYOTROPHIC LATERAL SCLEROSIS (ALS) IN HERCULANEUM AND JEFFERSON COUNTY, MISSOURI

Submitted by

Missouri Department of Health and Senior Services
Office of Epidemiology

March 2007

This study was supported by funds from the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) trust fund provided to the Missouri Department of Health and Senior Services under Cooperative Agreement Number U50/ATU772303-02 from the Agency for Toxic Substances and Disease Registry (ATSDR), Division of Health Studies, Health Investigations Branch, Program Announcement 02154: "Determining the Prevalence of Multiple Sclerosis and Amyotrophic Lateral Sclerosis in Communities Living Around Hazardous Waste Sites." Information about this grant is available in: Federal Register 2002; 67(112) June 11: 39991-39994.

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ABSTRACT

Background. An epidemiologic study of Amyotrophic Lateral Sclerosis (ALS) and Multiple Sclerosis (MS) was conducted in Jefferson County, Missouri to address concerns of residents in the town of Herculaneum that the existence of an active lead smelter in the area could have contributed to perceived excess of ALS and MS disease in the local population.

Methods. The study population consisted of the residents of Jefferson County, Missouri between 1998-2002. Data for the ascertainment of ALS and MS cases included inpatient and outpatient data, self-referrals, nursing home admissions, rehabilitation facilities, and death certificates. Patient data were abstracted by trained abstractors and reviewed by a consulting neurologist. The El Escorial criteria for ALS and Poser's criteria for MS were used to determine the diagnoses. The capture-recapture method was used to assess the completeness of case ascertainment. Spatial clustering was examined using a spatial scan statistic and performed with the SaTScan software. The Poisson distribution was assumed for the prevalence calculations and the cluster analysis. Crude and age-adjusted prevalence rates for ALS and MS were calculated.

Results. The case ascertainment level, as determined by the capture-recapture analysis, was 100% for ALS and 95% for MS. For ALS, the crude point prevalence in Jefferson County was 3.9 per 100,000 population (95% CI, 1.7 to 7.7) for the time point of December 31, 2002. After age-adjustment using the 2002 U.S. population as the standard, the point prevalence for ALS was 4.2 per 100,000 (95% CI, 1.9 to 6.6). The average annual ALS death rate was 2.3 per 100,000 persons. One significant cluster (p=0.04) of ALS cases was identified around the lead smelter.

For MS, the crude five-year period prevalence in Jefferson County was 105 per 100,000 population (95% CI, 91 to 121). The adjusted period prevalence, using the 2000 U.S. population

as the standard, was 107 per 100,000 (95% CI, 95 to 119). No significant spatial clusters of MS cases were identified around the lead smelter or anywhere in the study area. The prevalence estimates for both ALS and MS were comparable with those found elsewhere in other regions of the U.S. and in Western European countries.

Conclusions. The prevalence of ALS and MS in Jefferson County appeared to be comparable to that seen in recent years in other regions of USA and Western European countries. Because a significant cluster of ALS cases was identified around the lead smelter, detailed etiologic studies are needed to assess whether living in close proximity to a lead smelter is associated with the development of ALS.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is the most common form of motor neuron disease. It is characterized by progressive muscular weakness and a lethal outcome typically within 2-5 years after onset (1,2). The etiology of this devastating disease remains largely elusive, but may include genetic, environmental, infectious (i.e., viral, prion), and autoimmune processes (3).

Data from several countries have suggested that cases of ALS are spatially clustered (4-8). Unfortunately, many such reports involve a small number of cases and may suffer from under-ascertainment, and hence are unable to eliminate the possibility that these apparent ALS clusters could be due to chance alone (9,10). However, an investigation of 1000 ALS cases in Finland found convincing evidence of spatial clustering in southeast and south-central parts of the country (11) and studies in the United States have found higher ALS mortality rates in northwestern (12,13) and northern states (14). Taken together, these reports raise the possibility of an etiologic role for environmental factors. Other studies focused on environmental exposure to heavy metals and trace elements, such as mercury, manganese, selenium, aluminum, and especially lead, but have not conclusively identified these substances as causal risk factors (15-17). Even though no reliable scientific evidence linked heavy metal contamination in the environment to the incidence of ALS, communities with industries that generate such contamination continue to request public health investigations of perceived ALS clusters.

Multiple sclerosis (MS) is one of the most important neurological diseases by virtue of its frequency, chronicity, and tendency to attack young adults (18). Population-based estimates of MS prevalence in the United States ranged from 39 to 173 cases per 100,000 population (19).

The overall MS prevalence estimate based on The National Health Interview Survey during 1989 through 1994 is 85 per 100,000 population, higher than the 1976 estimate of 58 per 100,000 population (20). There are approximately 211,000 (± 20,000) persons with MS among the civilian, noninstitutionalized population in the U.S. according to this survey.

Despite progress in recent years in understanding this enigmatic disease, the etiology of MS remains largely unknown. While it is currently accepted that MS is an immune-mediated chronic inflammatory disorder of the central nervous system, genetic factors, infections, immunizations, physical and emotional stressors, climate, diet, and environmental factors may influence disease onset and outcome (21-23).

Prevalence of MS varies widely nationally and internationally. These variations have served as the basis for delineating the world into high-, medium-, and low-prevalence areas for MS (23). The disease is uncommon in tropical regions; its prevalence increases with higher latitudes north and south of the equator, a phenomenon known as the north-south gradient in the distribution of MS. However, epidemiologic studies conducted during the 1980s and 1990s in Europe and North America have showed changes in MS distribution over time, and the north-south gradient in prevalence appears to be diminishing (24,25). This observed “diffusion” of MS, along with the growing predominance among women and the changing prevalence by race, all suggest that environmental factors (e.g., persistent infection or toxin) play certain roles in the development of MS (25,26).

Substantial variation in the prevalence of MS has been observed even within the latitudinal gradient (27), supporting the possibility that environmental-factors may contribution to its geographic distribution. The documented change in risk of developing MS among people migrating in and out of high-prevalence areas also supports the environmental hypothesis. The

possible environmental hypothesis was also supported by the observation of several reported clusters of MS, perhaps related to trace metal (e.g., zinc, cadmium, chromium), organophosphates, and organic solvent exposure (28-32). Unfortunately, many of these studies involve only a small number of cases (< 40 individuals) with less than ideal case ascertainment. As a result, it is possible that those apparent clusters of MS may be due to chance alone (33). Further, animal studies show that lead exposure in animals could lead to production of autoantibodies against neural proteins; therefore lead may aggravate neurological disease such as MS by enhancing the immunogenicity of nervous system proteins (34).

This epidemiologic study of ALS and MS was conducted in response to concerns by residents of the town of Herculaneum, in Jefferson County, Missouri, where an active lead smelter has been in existence since 1892. The investigation by the Missouri Department of Health and Senior Services, supported by the U.S. Agency for Toxic Substances and Disease Registry (ATSDR), was prompted by specific reports of ALS in residents living near the smelter during the several years preceding the current investigation, and by other public health issues in the community. In addition to lead, the smelter produces copper, sulfuric acid, zinc, chromium, cobalt, cadmium, nickel, arsenic, and antimony, as a consequence of its manufacturing process. For a number of years the slag from the smelter was deposited into a waste management and a wetland area in Herculaneum, and the atmospheric and soil lead contamination in the area far exceeded levels considered to be environmentally safe (35).

STUDY OBJECTIVES

This study had three major objectives:

1. To identify ALS and MS cases through an aggressive case finding and ascertainment process.
2. To determine whether there was evidence of increased prevalence of ALS and MS in Jefferson County, Missouri.
3. To identify whether there was any spatial clustering of ALS and MS around the lead smelter or anywhere in Jefferson County.

SUBJECTS AND METHODS

Study population

The study population consisted of the residents of Jefferson County, Missouri where the smelter was located during the period of 1998 through 2002. The county had a population of 198,099 according to the 2000 census estimates and 203,791 according to the 2002 census estimates (36). Jefferson County is part of the larger St. Louis metropolitan area. It is a county with a mixed suburban and rural population; 97.5% of the residents are white non-Hispanic. Figure 1 displays map of the study area.

Data sources

Data used for ALS and MS case ascertainment included hospital inpatient data, emergency room and outpatient visits to neurologists and primary health care providers, self-

referrals, nursing home admissions, rehabilitation facilities, and death certificates. The Missouri Department of Health and Senior Services was the main, but not the only, source of the data. The state of Missouri has mandatory reporting of emergency department visits, hospitalizations, and deaths. Each of the hospitals at which potential cases of ALS or MS were treated, based on the state's databases, provided medical charts or microfilms for review. Additionally, these hospitals performed complete searches of their computer databases for ALS and MS cases during the study period to ensure completeness and accuracy of the state's databases.

All practicing neurologists in the St. Louis metropolitan area and all primary care providers in Jefferson County (a total of 255 physicians) were asked by direct mailing to participate in the study. All nursing home administrators in the St. Louis metropolitan area were also asked by direct mailing to participate. Participation in the study included providing names and charts for review of potential ALS or MS cases or informing us that no ALS or MS cases met the inclusion criteria. Self-referral of ALS and MS cases was encouraged through local newspaper advertisements, meetings with community representatives, direct mailings to members of the St. Louis Regional Chapter of the ALS Association, and the St. Louis Regional Chapter of the National MS Society, as well as ALS Association newsletters. Patients who were self-referred signed written authorization for review of their medical records to determine if they met the inclusion criteria.

Inclusion and exclusion criteria

Patients with diagnostic codes 335.20 or G12.2 (ALS) according to the 9^{th} or 10^{th} revision of the *International Classification of Diseases* were identified from the aforementioned data sources. The medical records and/or completed abstract forms of ALS cases were reviewed

by an expert neurologist specializing in neuromuscular diseases with over 25 years of experience. Diagnostic criteria in accord with the revised World Federation of Neurology El Escorial criteria for ALS diagnosis (37) were based on clinical evidence of a progressive neuromuscular disorder with combination of upper (UMN) and lower motor neuron (LMN) involvement in the same body regions. Patients with other motor neuron diseases, e.g., progressive muscular atrophy, progressive bulbar palsy, or multifocal motor neuropathy, and polyneuropathy were excluded. All potential ALS cases were assigned to one of five categories: 1) definite ALS, 2) probable ALS, 3) possible ALS, 4) undocumented probable/possible ALS, or 5) definitely not ALS. Cases in whom ALS was indicated as a primary cause of death on the death certificate were considered to be definite ALS.

MS cases were included in the study when they displayed symptoms compatible with MS, as confirmed by medical chart review. Patients with diagnostic codes 340 or G35 (MS) according to the 9th or 10th revision of the *International Classification of Diseases* were identified from the aforementioned data sources. Cases with onset of MS symptoms after the age of 60 years were not included in the study. Medical records or completed detailed abstract forms of randomly selected MS case-patients were reviewed by an expert neurologist and rated according to the Poser criteria (38) for MS diagnosis. All reviewed MS cases were assigned to one of five categories: 1) definite (clinical or laboratory supported), 2) probable (clinical or laboratory supported), 3) possible, 4) undocumented probable/possible, or 5) not MS.

Patients under consideration must have been residents of Jefferson County during at least part of the period between January 1, 1998 and December 31, 2002. The most recent address was used for identifying the location of patients with more than one address listed in the medical charts. Patients with street addresses in the medical record with ZIP codes at least partially in

Jefferson County were initially included in the study population. Some were subsequently excluded from the study population when it was determined by means of geocoding (described below) that they lived outside Jefferson County.

Data collection and quality assurance

Medical professionals specifically trained for ALS and MS chart abstraction completed the standardized medical record abstractions. For cases with multiple data sources, more than one chart was abstracted if additional information and data verification was required. Even if the additional medical chart was not abstracted, it was noted that more than one data source identified a specific ALS or MS case. More than 10% of medical records were randomly re-abstracted by a second staff member and verified by one of the investigators for ongoing quality assurance. No inaccuracies that could affect the assignment of ALS status were found during the medical chart reabstraction.

Geocoding

The street addresses of the MS and ALS cases and the lead smelter were converted to approximate geographic locations (latitude and longitude) using the Centrus GeoCoder for ESRI's ArcGIS (39,40). The resulting locations were then cross-referenced to a separate street file to ensure that the resulting location was near the associated road segment contained in the original case file. These locations were converted to one of 112 block groups in Jefferson County. Block groups are nested within counties and are comprised of about 1,500 persons on average. The lead smelter is located in the eastern part of Jefferson County. The coordinates are

in the Universal Transverse Mercator (UTM) projection, North American Datum 1983 (NAD83), Zone 15, and the units are measured in meters.

Assessment of the completeness of case identification

The capture-recapture analysis was used to assess the completeness of ALS case ascertainment. Three different data sources were used: hospital inpatient records, outpatient records, and death certificates. Outpatient data sources consisted of charts from neurologists and primary care providers. The capture-recapture method was used to evaluate MS case ascertainment as well. The completeness of ascertainment was estimated using three different data sources that, combined, accounted for more than 95% of MS cases: hospital records, outpatient records, and self-referral. Three different methods were used to calculate case ascertainment completeness and to estimate the number of ALS or MS cases that were not reported to any of the three data sources: the Petersen and Chapman estimates, the sample coverage approach, and log-linear modeling.

First, the Petersen and Chapman estimators are based on the dependence between two data sources. If the estimated population size from each pair of data sources varies significantly from the total number of ascertained cases, dependency among the two data sources likely exists. Underestimation of the total population size by the Peterson and Chapman method suggests positive dependence between the two data sources. Overestimation of the population size by both methods occurs when negative dependence between two data sources exists.

In the second method of case ascertainment completeness, the sample-coverage approach, dependence is modeled by a simple parameter known as the “coefficient of variation,” which measures the degree of dependence among two data sources (41). The sample coverage is

the average of the overlap fractions among data sources, which is the average of the fraction of cases found more than once. When dependence between data sources exists, the dependence was accounted for by adjusting the simple estimator with a fraction derived from a function of the two-sample coefficient of variation (41).

Third, log-linear modeling was used to identify the best model describing the relationships between the three data sources for ALS and MS cases (41,42). Interaction terms (relationships between data sources) was included by comparing a model with and one without relationships using the deviance value. Models with lower deviance show better fit. Based on the best model, the number of ALS and MS cases during 1998-2002 in Jefferson County that were not reported by any of the three data sources was calculate. The estimated number of missing ALS and MS cases was calculated based on formulae provided by Hook and Regal (42) and an interactive program (CARE, available at http://chao.stat.nthu.edu.tw/softwareCE.html). Adding the estimated number of missing cases to the observed number of cases resulted in the ascertainment-corrected number of ALS and MS cases.

Estimation of prevalence and death rates

The crude and age-adjusted point prevalence rates of ALS were estimated from those patients known to be alive and residing in Jefferson County on December 31, 2002. All residents of Jefferson County, Missouri, were included in the denominator for prevalence calculations based on the census estimate for 2002. Only definite and probable cases of ALS were included in the numerator. The ALS patient list was crosschecked with the death records in the state's vital statistics data system to identify deceased cases and calculated the ALS death rate for the study period.

Crude and age-adjusted period prevalence rates of MS were calculated from all case-patients residing in Jefferson County between January 1, 1998 and December 31, 2002. The total number of residents of Jefferson County, Missouri, based on Census 2000 estimates (mid-year for the study period), was included in the denominator for prevalence calculations. A Poisson distribution was assumed in calculating the 95% confidence intervals (CIs) for the prevalence estimates (43).

Spatial analysis

Spatial clustering of ALS and MS cases was evaluated separately using a spatial scan statistic performed with the software SaTScan (44,45). The statistic utilized a circular window of variable radius that moved across the map. The null hypothesis was that the prevalence of MS and ALS was the same in all windows, whereas the alternative hypothesis was that there was an elevation relative to outside the window. The process of cluster detection was run through 9,999 Monte Carlo permutations of the data set to identify combinations of clusters of elevated or reduced MS prevalence. The analyses were purely spatial with a maximum cluster size of 20% of the population size (or about 40,000 people). A Poisson distribution was assumed. The output provided the most likely cluster as well as several secondary clusters. Data associated with these clusters included the location identifiers, the search radius and center coordinates, relative risks, and a p-value based on the likelihood ratio test for each cluster. The cluster results were mapped using ArcGIS (version 9). The SatScan method was run with and once without prior knowledge of the location of the lead smelter. First, no specific focal points were assumed and the scans tested for both high and low clusters of ALS prevalence. Second, a specific focal point of elevated ALS or MS prevalence was assumed at the location of the lead smelter contained in a

special grid file. For MS analysis, both sets of scans were performed for the total population using age and sex as covariates, as well as the male and female cohorts. The size of the window's radius was allowed to vary. The SaTScan method was performed using Census Block Groups.

The Institutional Review Board of all the institutions involved approved the study protocol.

RESULTS

Case ascertainment

The study identified a total of 58 potential ALS cases, living and deceased, during 1998-2002 in Jefferson County through all data sources. During medical record review, the presence of ALS was not confirmed in nine cases identified from an electronic database whose diagnostic codes indicated ALS but whose medical records lacked any supporting data. These patients were excluded from data analysis. For an additional 10 cases, medical records indicated that the treating physicians established alternate diagnoses, including pseudobulbar palsy (three cases), myelopathy (two cases), cerebrovascular disease (one case), Becker's muscular dystrophy (one case), degenerative spinal stenosis (one case), myopathy (one case), and muscular dystrophy (one case). These cases were also excluded from the data analysis, leaving 39 living and deceased, "definite," "probable," and "possible" ALS cases meeting the study eligibility criteria. Of the 39 cases, three "definite" ALS cases were later excluded when the geocoding and mapping of their street addresses revealed that they lived outside of Jefferson County. The final analysis dataset contained 36 cases. Of the 36 living and deceased cases included in the study,

25 were classified as “definite,” five as “probable,” and six as “possible” ALS cases. Two cases (6%) occurred among members of the same family. All patients in the final database were white non-Hispanic: 25 men and 11 women (the male-to-female ratio was 2.3:1). The mean age at the time of the medical record review was 65 years (range, 39 to 84 years). Of the 36 cases in the final dataset, twenty-three patients died during the study period.

A total of 321 potential cases of MS were identified through all data sources. Of these cases, the presence of MS was not confirmed in 25 cases whose diagnostic codes indicated MS, but whose medical records did not support this diagnosis. An additional 20 cases aged 65 to 87 years were excluded from final analysis because interpretation of their symptoms was complicated by their advanced age. Those symptoms could not be assigned solely to MS without stronger supportive data in the medical record. For 28 cases, alternative diagnoses were established by the treating physician as indicated in the medical record: depression (7), sleep disorders (4), transitory ischemic attack (3), paralysis agitans (2), migraine (2), and one case each of stroke, cerebellar ataxia, rhythmic movements, congestive heart failure, atrial fibrillation, epilepsy, CNS vasculitis, narcolepsy, Alzheimer’s disease, and Crohn’s disease. These patients were excluded from final data analysis. Of the 248 MS patients who met the eligibility criteria, 38 were excluded when the geocoding of their street addresses revealed that they lived outside Jefferson County. The home addresses of an additional 2 patients could not be accurately mapped within the County and those cases were also excluded from the final dataset. The final dataset contained 208 patients, 56 of whom were randomly selected for review by a consulting neurologist: 48 were classified as “definite,” four as “probable,” and four as “possible” cases. Of the 208 case-patients, 202 were white non-Hispanic (97%), 4 were African-American (2%), one was Hispanic (0.5%) and one was Asian (0.5%). The mean age of study participants at the time

of chart review was 47.3 years (S.D. ± 10.1, range: 25-75); their median age was 47 years. Five patients included in the study died during the study period.

Completeness of case identification

Of the 30 "definite" or "probable" ALS cases, 29 (97%) were identified by inpatient data, outpatient data, or death certificates. Only one ALS case was identified by a nursing home and not by any other data source. Outpatient data was the most frequent identifying source for "definite" or "probable" ALS cases (70%), followed by death certificates (63%), and inpatient data (60%). The Petersen and Chapman population estimates for "definite" and "probable" ALS cases were somewhat higher than the overall number of ascertained ALS cases (n=29) when examining the death certificates and outpatient data (range: 35-45), suggesting dependence between these data sources. The Petersen and Chapman population size estimates were both 29, the same as the actually ascertained number of ALS cases based on death certificate and inpatient data sources, suggesting independence between these two data sources.

The sample coverage approach showed that the fraction of ALS cases found more than once was 87%. The estimated population size based on the high sample coverage was 27, which was lower than the total number of ALS cases ascertained. Based on the deviance value of the models, the best model was one that modeled the dependence between the outpatient data source with death certificates and with inpatient data. This model estimated that 29 ALS cases were present during 1998-2002 in Jefferson County using the combination of hospital records, outpatient records, and death certificates as data sources. This is 100% of ascertained cases (Table 1).

Of the 208 MS case-patients, 207 (99.5%) were identified by self-referral, hospital, or outpatient records. Only one MS case was identified by a nursing home and not by any other data source. There were no unique MS cases that were only identified by death certificate. Outpatient data (61%) and hospital records (60%) were almost equally common as a source for MS cases, followed by self-referrals (10%). Table 2 displays the various log-linear models used to assess completeness of MS case ascertainment. Based on the deviance, the best model was determined to be Model 6, which estimated that the completeness was 95% by using three data sources for identifying MS cases, namely hospital records, outpatient visits, and self-referrals. The estimated total number of MS cases was 218 (95% CI: 210 – 253); 11 MS cases were not reported by any of these three sources.

Prevalence and death rates of ALS

There were eight living ALS case-patients (six men and two women) in Jefferson County on December 31, 2002, of whom six were classified as “definite” and two as “probable” ALS. Based on these 8 cases, the crude point prevalence of ALS in Jefferson County was calculated to be 3.9 per 100,000 population (95% CI, 1.7 to 7.7). The prevalence was 5.0 per 100,000 population (95% CI, 2.2 to 9.8) for those aged 15 years or older. Table 3 summarized these results, and comparisons of these results with other ALS prevalence studies. The age-adjusted prevalence of ALS (using the 2002 U.S. population as the standard) was 4.2 per 100,000 (95% CI, 1.9 to 6.6). The prevalence of ALS increased with age. The average annual ALS death rate in Jefferson County was calculated to be 2.3 per 100,000 persons. For 21 of the 23 patients whose date of diagnosis and date of death were both available, the mean survival time from initial diagnosis to death was 28 months (range, 1 to 72 months; median: 25 months).

MS prevalence

There were 208 patients (168 women and 40 men, sex ratio 4.2:1) with MS in Jefferson County during the study period. The crude five-year period prevalence of MS in Jefferson County was 105 per 100,000 (95% CI, 91 to 121). It was 169 per 100,000 (95% CI, 145 to 197) for females and 41 per 100,000 (95% CI, 29 to 56) for males, as shown in Table 4, with comparisons to other MS prevalence studies. After age-adjustment using the 2000 U.S. population as the standard, the prevalence of MS was 107 per 100,000 (95% CI, 95 to 119). The age-specific prevalence for both sexes showed a peak in the 50-59 year age group (Figure 2).

ALS spatial clustering

Of the 30 "definite" and "probable" ALS cases identified in Jefferson County during 1998-2002, all were found within at least a census block group level of accuracy according to the match codes returned by the geocoder. These 30 cases were used to evaluate spatial clustering of ALS. One significant cluster (p=0.0436) was identified around the lead smelter, which included three ALS cases in three block groups (Figure 3). The expected number of ALS cases was 0.47, for a standardized prevalence ratio of 6.4 in this area. The most likely block group cluster independent of the smelter location had a p-value of 0.1970.

MS spatial clustering

Of the 208 MS cases in Jefferson County, 206 were found within at least a census block group level accuracy according to the match codes returned by the geocoder. These 206 cases were used to evaluate the spatial clustering of MS. Of the 206 cases, 166 were females and 40 were

males. The number of cases was higher in the northern part of the county, but the population density was higher in that area as well. No significant clusters were identified by any of the four SaTScan tests (Figure 4). The test with the lowest p-value (0.1788) resulted from a scan of only female cases that was focused on the lead smelter.

DISCUSSION

ALS study

The estimated point prevalence of ALS in Jefferson County, Missouri, was 3.9 (95% CI, 1.7 to 7.7) per 100,000 population. This estimate is similar to those reported in other countries, which range from 4.0 to 5.4 per 100,000 population (46-48). The prevalence found in this study is higher than the prevalence of ALS reported in Harris County, Texas (3.0 per 100,000; 95% CI, 2.5 – 4.0) (59). This discrepancy could be due to the relatively low case capture rate (69%) in the Harris County study (60). If the capture rate in that study had been 100%, the estimated crude prevalence would have been close to the rate in the present study. A study of ALS prevalence by Traynor et al. (46) using the ongoing ALS register in Ireland, which has a 100% case ascertainment, found a point prevalence that was very close to that found in this study.

Data from several countries have suggested that cases of ALS are spatially clustered (6,47,61). In a large study of spatial clustering of ALS, Sabel et al. found convincing evidence of clustering in Southeast Finland (11). Since there was consistency in the location of clusters based on the place of birth and place of death, the authors concluded that either genetic or environmental influences were possible explanations for the observed clustering. In the present study a small spatial cluster of ALS cases was found within a three-mile radius from the lead smelter, where three cases were actually observed while only 0.47 ALS cases were expected.

Previous studies have suggested lead exposure as a potential environmental risk factor for ALS (62-64). Lead can exert neurotoxicity through mitochondrial damage and oxidative damage to neural tissue (65). However, caution needs to be exercised in interpreting findings of the ALS study. First, this study was not designed to study risk factors for ALS; therefore it was not possible to evaluate what factors may be associated with ALS in the area. For example, immigration of persons previously exposed to risk factors for ALS into the area around the lead smelter could be able to explain the cluster. Second, clusters based on prevalent cases may be more related to disease survival than to the development of the disease. Third, recently published studies have found that self-reported occupational exposure to lead was more important than residential or recreational exposure as a risk factor for ALS (65). However, the present study did not collect information about occupational history, hence was unable to test this hypothesis. Forth, the ALS cluster detected in this study was based on the small sample of ALS cases.

This study has several strengths. First, it used the El Escorial criteria for ALS diagnosis, which decreased the possibility of overestimation of ALS prevalence and facilitated comparisons with similar studies around the world. Second, this study used the capture-recapture method to show that the completeness of case ascertainment of “definite” and “probable” ALS cases was nearly 100%. Third, the geographic information system (GIS) technique was used in this study to approximate the location of the ALS cases. While this is still an approximation, the use of GIS greatly enhances the accuracy of geographically locating ALS cases. Had the ZIP codes been used for cluster detection, three ALS cases outside of Jefferson County would have been erroneously included in the analysis, since ZIP codes can cross county boundaries.

In summary, in Jefferson County, Missouri, the prevalence of ALS appears to be comparable to that seen in Western European countries in recent years. A small cluster of ALS cases consisting of three cases was found in the vicinity of the lead smelter.

MS study

In this study of MS aggressive case-finding methods were used to identify all cases in Jefferson County, Missouri, to estimate the prevalence of MS. The crude prevalence of MS in the county was 105 per 100,000, which was well within the range of prevalence estimates reported in recent years, as shown in Table 4. In addition, no significant geographical clustering of MS cases was found in this study.

At least three methodological considerations should be noted when comparing the prevalence estimates in this study with MS prevalence in other studies (shown in Table 4). First, this study estimated the period prevalence as opposed to the point prevalence in other studies. The period prevalence was chosen to be consistent with several ongoing studies in Illinois, Massachusetts, Washington and Texas, to facilitate direct comparison of prevalence from different regions of the country. Second, using the capture-recapture method, the completeness of case ascertainment in this study was shown to be 95%; hence significant underestimation of prevalence was unlikely. Third, geocoding was used to approximate the locations of MS cases. Had the inclusion criteria been based on zipcode information, 38 MS cases outside of Jefferson County would have been erroneously included in the analysis because some zipcodes cross county boundaries.

MS clustering has been reported from previous studies as indicated earlier. However, most of those studies had significant methodological limitations; hence detected clusters may have not been “true” clusters. A study in Tayside, Scotland was the only known investigation of

MS clustering using the spatial scan statistics, allowing for more robust analysis of disease clustering (58). In a study of all incident cases of MS from 1970 to 1997, the authors were able to detect a significant temporal cluster for the whole region and spatial-temporal cluster in the south-west part of that region. The present study did not focus on the area surrounding the lead smelter only; instead, a search of MS clusters was conducted in the entire Jefferson County, assuming all county residents were at risk for MS. This approach allowed for a comprehensive assessment of possible MS clustering in the study area using spatial scan statistic. The SatScan method was run with and without prior knowledge of the location of the lead smelter, using age and sex as covariates. Neither methods had detected any significant spatial clusters of MS. Analysis of male and female case-patients separately also did not find any significant MS clustering in the Jefferson County.

At least three limitations should be considered in interpreting the findings of the MS study. First, this study is based on prevalent cases rather than incident cases. Clusters based on prevalent cases may be influenced by disease survival. Second, emigration from the study area of persons exposed to potential risk factors for MS could have affected this study's ability to detect MS clusters. According to the 2000 census, 56% of residents in Jefferson County were living in the same house from 1995 to 2000. This percentage is close to the 53.6% in the entire state of Missouri. Third, searching for cases for five years may not be sufficient for MS because this disease may have a long induction period (66), resulting in a slow accumulation of cases in the study area.

In summary, in Jefferson County, Missouri, the prevalence of MS appears to be in line with prevalence estimates reported recently in the scientific literature. The perceived excess of MS cases by residents of the county may reflect a worldwide trend of increasing MS prevalence.

CONCLUSIONS

The prevalence of ALS and MS in Jefferson County, Missouri is comparable to that seen in recent years in other areas of the United States and the Western Europe. A small cluster of ALS was detected in the proximity of a lead smelter. This study was not designed to study risk factors for ALS; therefore it was unable to evaluate what factors may be associated with ALS in the area. No spatial clustering of MS in the county was detected.

RECOMMENDATIONS

Implementation of an ALS registry should be considered for the St.Louis Metropolitan area. Such incident registry could be used to estimate the burden of ALS, and determine whether increases of ALS over time and geographical area are occurring. The outpatient and inpatient data and death certificates would provide for a comprehensive system to identify ALS cases for the registry. An etiologic study of ALS in the Herculaneum, Missouri, area should be considered to determine the risk factors for this disease in this population.

ACKNOWLEDGEMENTS

The St. Louis Regional Chapter of ALS Association and the St. Louis Regional Chapter of the National MS Society provided valuable assistance for this study. The participation of area neurologists helped made this study possible. The scrupulous work of chart abstractors was indispensable for the success of this study. The federal Agency for Toxic Substances and

Disease Registry, Centers for Disease Control and Prevention, provided funding for this study and reviewed its findings.

REFERENCES

1. Guiloff RJ, Goonetilleke A. Natural history of amyotrophic lateral sclerosis: Observations with the Charing Cross Amyotrophic Lateral Sclerosis rating scales. In Serratrice G, Munsat T Pathogenesis and Therapy of Amyotrophic lateral Sclerosis. Philadelphia: Lippincott-Raven, 1995, pp185-198.

2. del Aguila MA, Longstreth WT Jr, McGuire V, Koepsell TD, van Belle G. Prognosis in amyotrophic lateral sclerosis: a population-based study. Neurology 2003; 60: 813-9.

3. Rowland LP, Shneider NA. Amyotrophic lateral sclerosis. N Engl J Med 2001; 344: 1688-700.

4. Hyser CL, Kissel JT, Mendell JR. Three cases of amyotrophic lateral sclerosis in a common occupational environment. J Neurol 1987; 234: 443-4.

5. Melmed C, Krieger C. A cluster of amyotrophic lateral sclerosis. Arch Neurol 1982; 39: 595-66.

6. Mitchell JD, Gibson HN, Gatrell A. Amytrophic Lateral Sclerosis in Lancashire and South Cumbria, England, 1976-1986. Arch Neurol 1990; 47:875-80.

7. Sienko DG, Davis JP, Taylor JA, Brooks BR. Amyotrophic lateral sclerosis. A case-control study following detection of a cluster in a small Wisconsin community. Arch Neurol 1990; 47: 38-41.

8. Corcia P, Jafari-Schluep HF, Lardillier D, et al. A clustering of conjugal amyotrophic lateral sclerosis in southeastern France. Arch Neurol 2003; 60: 553-7.

9. Malaspina A, Alimonti D, Poloni TE, Ceroni M. Disease clustering: the example of ALS, PD, dementia and hereditary ataxias in Italy. Funct Neurol 2002; 17: 177-82.

10. Armon C. Environmental risk factors for amyotrophic lateral sclerosis. Neuroepidemiology 2001; 20: 2-6.

11. Sabel CE, Boyle PJ, Loytonen M, et al. Spatial clustering of Amyotrophic Lateral Sclerosis in Finland at place of birth and place of death. Am J Epidemiol 2003; 157:898-905.

12.Betemps EJ, Buncher CR. Birthplace as a risk factor in motor neurone disease and Parkinson's disease. Int J Epidemiol 1993; 22: 898-904.

13. Noonan CW, White MC, Thurman D, Wong LY. Temporal and geographic variation in United States motor neuron disease mortality, 1969-1998. Neurology 2005; 64: 1215-21.

14. Sejvar JJ, Holman RC, Bresee JS, Kochanek KD, Schonberger LB. Amyotrophic Lateral Sclerosis mortality in the United States, 1979-2001. Neuroepidemiology. 2005; 25: 144-52.

15. Armon C. An evidence-based medicine approach to the evaluation of the role of exogenous risk factors in sporadic amyotrophic lateral sclerosis. Neuroepidemiology 2003; 22: 217-28.

16. Bergomi M, Vinceti M, Nacci G, et al. Environmental exposure to trace elements and risk of amyotrophic lateral sclerosis: a population-based case-control study. Environ Res 2002; 89: 116-23.

17. Guidetti D, Bondavalli M, Sabadini R, et al. Epidemiological survey of amyotrophic lateral sclerosis in the province of Reggio Emilia, Italy: influence of environmental exposure to lead. Neuroepidemiology. 1996;15:301-12.

18. Multiple sclerosis and allied demyelinative diseases. In: Ropper AH, Brown HR, editors. Principles of Neurology. 2005; 771-790

19. Jacobson DL, Gange SJ, Rose NR, Graham NM. Epidemiology and estimated population burden of selected autoimmune diseases in the United States. Clin Immunol Immunopathol. 1997 Sep; 84(3): 223-43.

20. Noonan CW, Kathman SJ, White MC. Prevalence estimates for MS in the United States and evidence of an increasing trend for women. Neurology. 2002 Jan 8; 58(1): 136-8.

21. Ruth AM. Evironmental risk factors in multiple sclerosis aetiology. Lancet Neurol 2004 Dec; 3(12): 709-18. Review.
22. Callander M, Landtblom AM. A cluster of multiple sclerosis cases in Lysvik in the Swedish county of Varmland. Acta Neurol Scand. 2004 Jul; 110(1): 4-22.
23. Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. N Engl J Med. 2000 Sep 28; 343(13): 938-52. Review.
24. Rosati G. The prevalence of multiple sclerosis in the world: an update. Neurol Sci. 2001 Apr; 22(2): 117-39. Review.
25. Kurtzke JF. Epidemiology and etiology of multiple sclerosis. Phys Med Rehab Clin N Am. 2005; 16: 327-49
26. Landtblom AM, Riise T, Kurtzke JF. Further considerations on the distribution of multiple sclerosis in Sweden. Acta Neurol Scand. 2005 Apr; 111(4): 238-46.
27. Beck CA, Metz LM, Svenson LW, Patten SB. Regional variation of multiple sclerosis prevalence in Canada. Mult Scler. 2005 Oct; 11(5): 516-9.
28. Stein EC, Schiffer RB, Hall WJ, Young N. Multiple sclerosis and the workplace: report of an industry-based cluster. Neurology. 1987 Oct; 37(10): 1672-7
29. Schiffer RB, McDermott MP, Copley C. A multiple sclerosis cluster associated with a small, north-central Illinois community. Arch Environ Health. 2001 Sep-Oct; 56(5): 389-95.
30. Ingalls TH. Clustering of multiple sclerosis in Galion, Ohio, 1982-1985. Am J Forensic Med Pathol. 1989 Sep; 10(3): 213-5.
31. Krebs JM, Park RM, Boal WL. A neurological disease cluster at a manufacturing plant. Arch Environ Health. 1995 May-Jun; 50(3):190-5.
32. Landtblom AM, Flodin U, Soderfeldt B, et al. Organic solvents and multiple sclerosis: a synthesis of the current evidence. Epidemiology. 1996 Jul; 7(4): 429-33.
33. Williamson DM, Henry PJ. Challenges in addressing community concerns regarding clusters of multiple sclerosis and potential environmental exposures. Neuroepidemiology. 2004; 23: 211-16
34. Waterman SJ, el-Fawal HA, Snyder CA. Lead alters the immunogenicity of two neural proteins: a potential mechanism for the progression of lead-induced neurotoxicity. Environ Health Perspect. 1994 Dec; 102(12): 1052-6

35. Missouri Department of National Resources. Herculaneum lead contamination. www.dnr.mo.gov/env/herc.htm

36. U.S. Census 2000. www.census.gov 18. Missouri Depatmernt of National Resources. Herculaneum lead contamination. www.dnr.mo.gov/env/herc/herc.htm. Accessed March, 2005

37. El Escorial revisited: revised criteria for the diagnosis of Amyotrophic Lateral Sclerosis. Consensus conference, Warrenton, Virginia, April 2-4,1998.

38. Poser CM, Paty DW, Scheinberg LC, et al. New diagnostic criteria for multiple sclerosis: Guidelines for research protocols. Ann Neurol, 1983; 13: 227-31

39. ESRI: ArcGIS 9.0. http://www.esri.com/, 2004

40. Group1: Centrus GeoCoder for ESRI ArcGIS. http://www.g1.com/, 2005.

41. Chao A, Tsay PK, Lin SH, Shau WY, Chao DY. The applications of capture-recapture models to epidemiological data. Stat Med 2001; 20:3123-57.

42. Hook EB, Regal RR. Capture-recapture methods in epidemiology: methods and limitations. Epidemiol Rev 1995;17: 243-64.

43. Schoenberg BS. Calculating confidence intervals for rates and ratios. Simplified method utilizing tabular values based on Poisson distribution. Neuroepidemiology 1983; 2:257-265.

44. Kulldorff M. A spatial scan statistic. Communications in Statistics: Theory and Methods, 26:1481-1496, 1997.

45. Kulldorff M. and Information Management Services, Inc. SaTScanTM v5.1.1: Software for the spatial and space-time scan statistics. http://www.satscan.org/, 2005*.

46. Traynor BJ, Codd MB, Corr B, Forde C, Frost E, Hardiman O. Incidence and prevalence of ALS in Ireland, 1995-1997. Neurology 1999; 52:504-9.

47. Mandrioli J, Faglioni P, Merelli E, Sola P. The epidemiology of ALS in Modena, Italy. Neurology 2003; 60:683-9.

48. Nygren I, Antonova K, Mattsson P, Askmark H. The ALS/MND prevalence in Sweden estimated by riluzole sales statistics. Acta Neurol Scand 2005; 111:180-4.

49. Agency for Toxic Substances and Disease Registry. Multiple Sclerosis Pilot Surveillance 19 1Texas Counties. Atlanta, GA: US Department of Health and Human Services, Public Health Service, 2004.

50. Modrego PJ, Pina MA Trends in prevalence and incidence of multiple sclerosis in Bajo Aragon, Spain. J Neurol Sci. 2003 Dec 15; 216(1): 89-93.

51. Nicoletti A, Patti F, Lo Ferno S, et al. Possible increasing risk of multiple sclerosis in Catania, Sicily. Neurology. 2005 Oct 25; 65(8): 1259-63.

52. Sloka JS, Pryce-Phillips WE, Stefanelli M. Multiple sclerosis in Newfoundland and Labrador--a model for disease prevalence. Can J Neurol Sci. 2005 Feb; 32(1): 43-9.

53. Agency for Toxic Substances and Disease Registry. Multiple Sclerosis Among Lorain County, Ohio, Residents 1998–2000. Atlanta, GA: US Department of Health and Human Services, Public Health Service, 2005.

54. Neuberger JS, Lynch SG, Sutton ML, et al. Prevalence of multiple sclerosis in a residential area bordering an oil refinery. Neurology. 2004 Nov 23; 63(10): 1796-802.

55. Fox CM, Bensa S, Bray I, Zajicek JP. The epidemiology of multiple sclerosis in Devon: a comparison of the new and old classification criteria. J Neurol Neurosurg Psychiatry. 2004 Jan; 75(1):56-60.

56. Dahl OP, Aarseth JH, Myhr KM, et al. Multiple sclerosis in Nord-Trondelag County, Norway: a prevalence and incidence study. Acta Neurol Scand. 2004 Jun; 109(6): 378-84.

57. Mayr WT, Pittock SJ, McClelland RL, et al. Incidence and prevalence of multiple sclerosis in Olmsted County, Minnesota, 1985-2000. Neurology. 2003; 61:1373-7

58. Donnan PT, Parratt JD, Wilson SV, et al. Multiple sclerosis in Tayside, Scotland: detection of clusters using a spatial scan statistic. Mult Scler. 2005 Aug; 11(4): 403-8.

59. Annegers JF, Appel S, Lee J, Perkins P. Incidence and prevalence of Amytrophic Lateral Sclerosis in Harris County, Texas, 1985-1988. Arch Neurol 1991; 48:589-93.

60. McCarty DJ, Tull ES, Moy CS, Kwoh CK, LaPorte RE. Ascertainment corrected rates: applications of capture-recapture methods. Int J Epidemiol 1993; 22: 559-65.

61.Taylor J, Davis J. Evidence for clustering of Amyotrophic lateral sclerosis in Wisconsin. J Clin Epidemiol 1989; 42: 569-75.

62. Chancellor AM, Slattery JM, Fraser H, Warlow CP. Risk factors for motor neuron disease: a case-control study based on patients from the Scottish Motor Neuron Disease Register. J Neurol Neurosurg Psychiatry 1993; 56: 1200-6.31.

63. Strickland D, Smith SA, Dolliff G, Goldman L, Roelofs RI. Amyotrophic lateral sclerosis and occupational history. A pilot case-control study. Arch Neurol. 1996; 53:730-3.

64. Mitchell JD. Amyotrophic lateral sclerosis: toxins and environment. Amyotroph Lateral Scler Other Motor Neuron Disord 2000; 1: 235-50.

65. Kamel F, Umbach D, Munsat T, Shefner JM, Hu H, Sandler DP. Lead exposure and Amytrophic Lateral Sclerosis. Epidemiology 2002; 13:311-9.

66. Wolfson C, Wolfson DB. The latent period of multiple sclerosis: a critical review. Epidemiology. 1993; 4: 464-70

TABLES

Table 1. Loglinear models for combinations of outpatient, inpatient, and death certificate for ALS data sources.

Model	d.f.	Dev	x	Nhat	s.e.	95% CI	Completeness
1. Independent data sources	3	6.81	2	31	2	30 - 39	94
2. outpatient, inpatient, DC, inpatient* outpatient	2	2.23	1	30	1	29 - 35	97
3. outpatient, inpatient, DC, DC * inpatient	2	6.12	3	32	3	30 - 45	91
4. outpatient, inpatient, DC, DC * outpatient	2	5.91	1	30	2	29 - 38	97
5. outpatient, inpatient, DC, inpatient * outpatient, outpatient * DC	1	0.42	0	29	1	29 - 34	100
6. outpatient, inpatient, DC, inpatient * outpatient, inpatient * DC	1	2.14	1	30	1	29 - 37	97
7. outpatient, inpatient, DC, outpatient* DC, inpatient * DC	1	5.64	2	31	3	29 - 43	94

d.f.: degree of freedom; Dev: Deviance; x: estimated number of nonreported cases; Nhat: total number of estimated cases (including underreported cases); D.C.: death certificate data source.
* denotes the association between data sources; s.e.: standard error

Table 2. Loglinear models for combinations of outpatient and inpatient data sources, and self-referral for MS cases.

Model	d.f.	Dev	Nhat	s.e.	95% CI	Completeness	x
1. Independent data sources	3	15.25	307	23	270 - 364	67.4	100
2. outpt, hospital, self, hosp*outpt	2	6.75	227	15	212 - 283	91.2	20
3. outpt, hospital, self, self*hospital	2	14.58	301	23	266 - 359	68.8	94
4. outpt, hospital, self, self*outpt	2	2.24	334	31	287 - 410	62.0	127
5. outpt, hospital, self, hosp*outpt, outpt* self	1	1.21	259	49	218 - 452	79.9	52
6. outpt, hospital, self, hospital*outpt, hospital*self	**1**	**1.34**	**218**	**9**	**210 - 253**	**95.0**	**11**
7. outpt, hospital, self, outpatient*self, hospital*self	1	2.01	330	31	282 - 407	62.7	123
8. outpt, hospital, self, hosp*outpt, outpt*self, hospital*self	0	0.00	234	31	212 - 367	88.5	27

d.f.: degree of freedom; Dev: Deviance; x: estimated number of nonreported cases; Nhat: total number of estimated cases (including underreported cases). The best model is listed in bold font.

Table 3. Comparison of ALS prevalence (per 100,000 population) from the epidemiologic studies using El Escorial diagnostic criteria with Jefferson County, Missouri, USA

Country	**Calculation year(s)**	**Crude (95% CI)**	**15 years and older (95%CI)**
Republic of Ireland (46)	1996	4.7 (4.0-5.5)	6.2 (5.3-7.1)
Modena, Italy (47)	1990-1999	4.0	
Sweden (48)	2003*	5.4	6.2† (5.7-6.8)
Jefferson County, Missouri, USA	2002	3.9 (1.7-7.7)	5.0 (2.2-9.8)

* ALS/MND (motor neuron disease) data

† Estimated by authors based on published prevalence data and population census data

Table 4. Comparison of Multiple sclerosis prevalence (per 100,000 population) from published epidemiologic studies with Jefferson County, Missouri, USA

Country	Year of calculation	Crude prevalence (95% CI)	Latitude
Lubbock area, Texas, USA (49)	1998-2000	42.8 (36.8-49.5)*	33.3 N
Bajo Aragon, Spain (50)	2003	75 (52-97)	41.5 N
Catania, Italy (51)	1999	92.0 (81.8-103.2)	37.5 N
Newfoundland/Labrador, Canada (52)	2001	94.4 (90.2-98.7)	46-61 N
Jefferson County, Missouri, USA	1998-2002	105 (91-121)*	38.25 N
Lorain County, Ohio, USA (53)	1998-2000	112.4 (99.8-125)*	41.24 N
Sugar Creek, Missouri, USA (54)	1998-2001	113 (93-136)*	39.11 N
Devon, United Kingdom (55)	2001	117.6 (106.1-129.1)	50.5 N
Nord-Trondelag, Norway (56)	2000	163.6 (142.2.0-187.5)	64 N
Olmsted County, Minnesota, USA (57)	2000	176.6	44 N
Tayside, Scotland, UK (58)	2002	236 (221-251)	56 N

1 * Denotes period prevalence

FIGURES

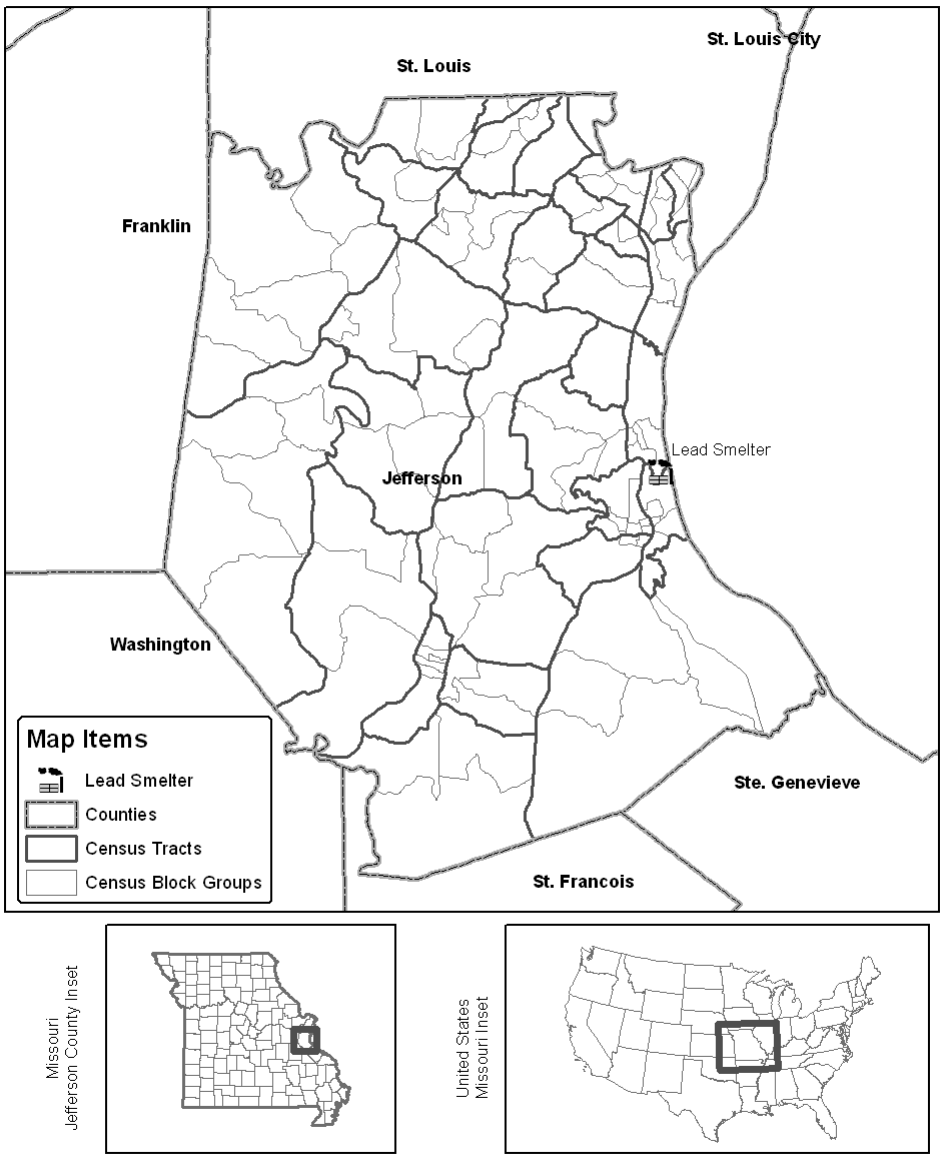

Figure 1. Map of Jefferson County, Missouri

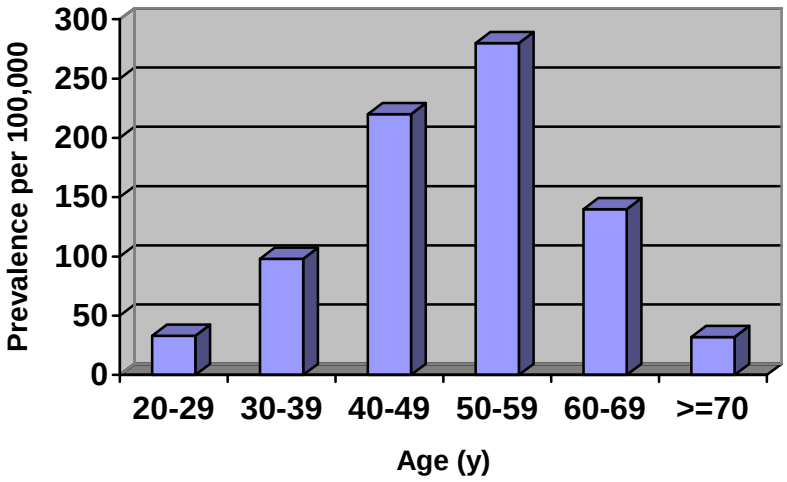

Figure 2. Age-specific prevalence of multiple sclerosis: Jefferson County, Missouri, 1998-2002

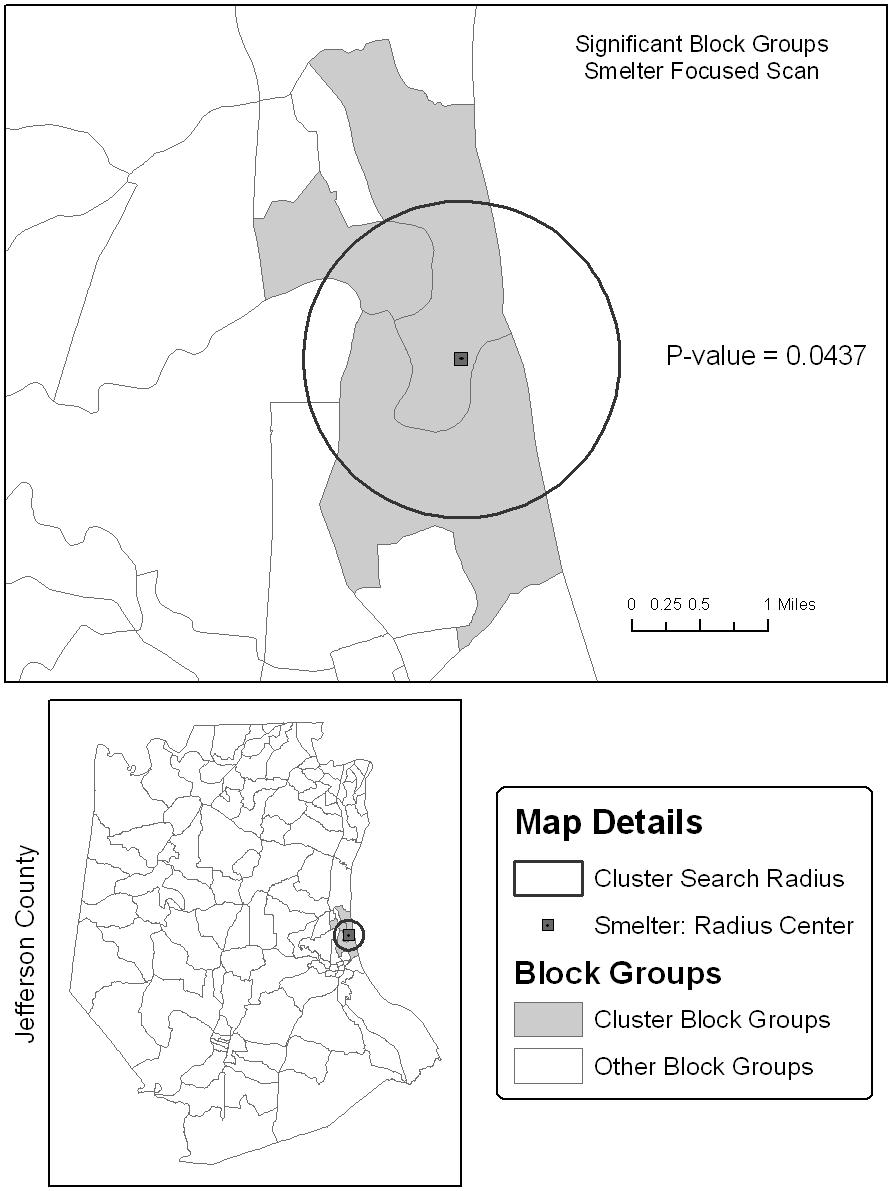

Figure 3. SaT Scan analysis of the geographic distribution of ALS cases: Jefferson County, Missouri, 1998-2002

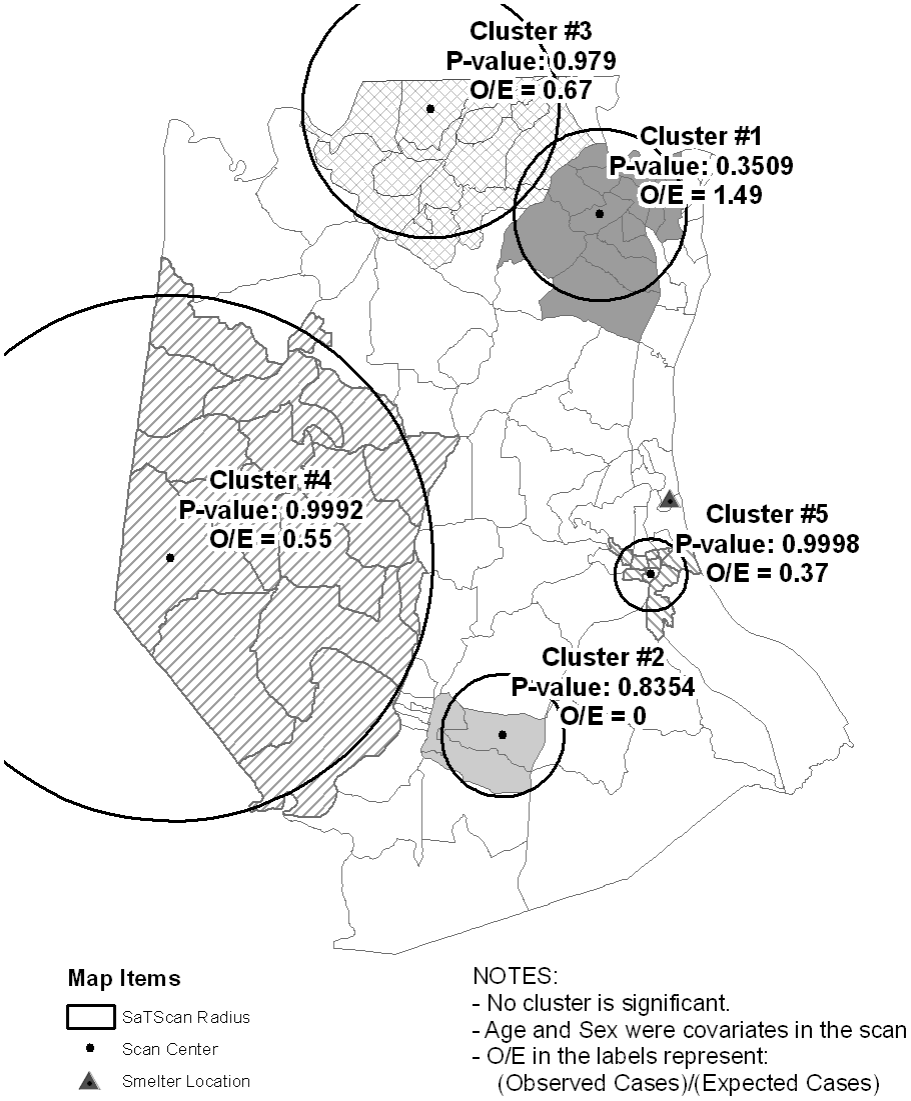

Figure 4. SaT Scan analysis of the geographic distribution of MS cases: Jefferson County, Missouri, 1998-2002

APPENDICES

A. Fact Sheets

Multiple Sclerosis Prevalence Study Herculaneum, Jefferson County, Missouri

What was the purpose of this study?

The purpose of this study was to identify all persons with multiple sclerosis (MS) living in Jefferson County, Missouri

Why was this study done?

This study was done to respond to concerned residents about the number of persons with MS in the Herculaneum area. Community residents are concerned about the impact of releases from an active lead smelter in their community.

Who conducted this study?

This study was conducted by the Missouri Department of Health & Senior Services with funding from the Agency for Toxic Substances and Disease Registry, a public health agency located in Atlanta, Georgia.

What is multiple sclerosis?

MS is a chronic disease that steadily weakens the central nervous system. MS affects nerve fibers found in the brain and spinal cord. The inflammation of nervous tissue causes the loss of myelin. Myelin is a fatty material that protects the nerve fibers in the brain and spinal cord. With the loss of myelin, many areas of scar tissue (sclerosis) are formed along the covering of the nerve cells causing the messages to and from the brain to be altered.

What is the cause of MS?

The cause of MS is not known. Factors that may affect the onset and outcome of MS are: climate, diet, environment, family, physical and emotional stress, infections, and vaccines. MS is more common in women and in Caucasians. The average age of onset is between 18 and 35

years.

How many people have MS?

MS affects between 250,000 – 400,000 persons in the U.S. It is estimated that there are 39 to 173 patients with MS for every 100,000 people in the U.S.

How was this study conducted?

1. Participant Selection

   Persons with MS were identified by:
   - Reviewing existing records from hospitals, emergency room and office visits, nursing home admissions, rehabilitation facilities, and death certificates;
   - Mailing to all practicing doctors in neurology, primary care providers and nursing home administrators; and
   - Confirming self-referrals of persons with MS.

2. The inclusion criteria required all of the following to be a study participant:
   - Residence in Jefferson County;
   - Clinical visits between January 1, 1998 and December 31, 2002; and
   - Confirmed diagnosis of possible, probable, or definite MS by Neurology doctor

3. Data Collection and Quality Assurance
   - Medical records were reviewed by trained medical professionals and neurology specialist to confirm diagnosis of MS.

4. Mapping of Cases
   - Using special computer program the street addresses of all persons with confirmed MS diagnosis were mapped on the Jefferson County map in order to identify any unusual accumulation of cases in one area.

What were the main findings of the study?

The main findings of this study are:

1. The prevalence of MS in Jefferson County was 105 per 100,000 populations, or in other words, there were 105 people with MS for every 100,000 residents of Jefferson County.
2. The majority of people with MS were women and white non-Hispanic.
3. The median age of the study participant was 47 years, which means that half of all cases were younger than 47 years, and the other half was older than 47 years.
4. MS among women was 169 per 100,000 and among men were 41 per 100,000.
5. The age group with the highest occurrence for MS was 50 to 59 years.
6. The number of persons with MS in Jefferson County was not unusual, when compared to

other areas of the U.S. or around the world.

What are the limitations of this study?

The limitations of this study are:

1. This study did not capture those persons with MS who moved away from Jefferson County and later developed MS;
2. This study was limited to a 5-year period.

What follow-up activities are planned?

The Missouri Department of Health & Senior Services is working with the Agency for Toxic Substances and Disease Registry to possibly be involved in a study to investigate the role of environmental exposures and genetic susceptibility in the development of MS.

Who can I contact if I want more information?

For more information, contact:

Bao-Ping, Zhu, MD
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ALS Prevalence Study
Herculaneum, Jefferson County, Missouri

What was the purpose of this study?

The purpose of this study was to identify all persons with Amyotrophic Lateral Sclerosis (ALS), also known as Lou Gehrig's disease living in Jefferson County, Missouri.

Why was this study done?

This study was done to respond to concerned residents about the number of persons with ALS in the Herculaneum area. Community residents are concerned about the impact of releases from an active lead smelter in their community.

Who conducted this study?

This study was conducted by the Missouri Department of Health & Senior Services with funding from the Agency for Toxic Substances and Disease Registry, a public health agency located in Atlanta, Georgia.

What is ALS?

ALS is characterized by progressive muscle weakness in the entire body, and a lethal outcome typically within 2-5 years after onset.

What is the cause of ALS?

The cause of this devastating disease remains largely unknown, but may include genetic, environmental, infectious, and autoimmune processes. The disease is rare before age 40, but increases with advancing age, peaking at around age 70.

How many people have ALS?

ALS is a rare disease. It is estimated that there are 4 to 6 patients with ALS for every 100,000 people in the U.S. and other countries.

How was this study conducted?

5. Participant Selection

Persons with ALS were identified by:

- Reviewing existing records from hospitals, emergency room and office visits, nursing home admissions, rehabilitation facilities, and death certificates;
- Mailing to all practicing doctors in neurology, primary care providers and nursing home administrators; and
- Confirming self-referrals of persons with ALS.

6. The inclusion criteria required all of the following to be a study participant:
    - Residence in Jefferson County;
    - Clinical visits between January 1, 1998 and December 31, 2002; and
    - Confirmed diagnosis of possible, probable, or definite ALS by Neurology doctor

7. Data Collection and Quality Assurance
    - Medical records were reviewed by trained medical professionals and neurology specialist to confirm diagnosis of ALS.

8. Mapping of Cases
    - Using special computer program the street addresses of all persons with confirmed ALS diagnosis were mapped on the Jefferson County map in order to identify any unusual accumulation of cases in one area.

What were the main findings of the study?

The main findings of this study are:

7. The prevalence of ALS in Jefferson County was 3.9 per 100,000 population, or in other words, there were about 4 people with ALS for every 100,000 residents of Jefferson County.
8. The majority of people with ALS were men and white non-Hispanic.
9. The mean age of the patients with ALS was 65 years.
10. The age group with the highest occurrence for ALS was older than 75 years.
11. The number of persons with ALS in Jefferson County was not unusual, when compared to other areas of the U.S. or around the world.
12. There was an accumulation of cases identified around the lead smelter, which included three ALS patients.

What are the limitations of this study?

The limitations of this study are:

1. This study was not designed to study risk factors for ALS; therefore we cannot evaluate what factors may be associated with ALS in the Herculaneum area.

2. This study did not capture those persons with ALS who moved away from Jefferson County and later developed ALS.

3. The accumulation of ALS cases detected in the study was based on the small number of ALS patients .

What follow-up activities are planned?

The Missouri Department of Health & Senior Services, in collaboration with the Agency for Toxic Substances and Disease Registry and other state health departments, has submitted a grant to the National Institutes of Health (NIH) to conduct a study to investigate whether lead exposure is associated with the development of ALS.

Who can I contact if I want more information?

For more information, contact:

Bao-Ping, Zhu, MD
State Epidemiologist, Missouri Department of Health & Senior Services, 930 Wildwood, P.O. Box 570 Jefferson City, MO, 65102-0570; Tel: (573) 751-6128, Email: BaoPing.Zhu@dhss.mo.gov

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B. Sample Medical Record Abstract Forms

Amyotrophic Lateral Sclerosis Abstraction Form

Appendix E

Patient Information:

Medical Record #: _____ **Case #:** _____ **Social Security #:** _____

Name: _____ _____ _____

Last First MI Maiden

Home Address: _____ **City**: _____

State: _____ **Zip:** _____ **County:** _____ **Date of Birth**: ____/____/_____

DD MM YYYY

Race/Ethnicity: *(check one)* o African American o Asian o Pacific Islander **Sex:** *(check one)* o Female o Male

o Hispanic/Latino o White o American Indian o Other_____

Occupation When First Diagnosed:_____

Case Referred From: *(check one)*

o Neurologist o Other Physician Office o CHIIME/DHSS Database Passive Surveillance

o Hospital DRG Active Surveillance o Pharmacy Active Surveillance o Patient Self Referral

o Community Advocacy Group o Home Nursing Care Agency

Physician Information:

Initial Diagnosing Physician: _____ **Phone Number:** _____

Address: _____ **City**: _____ **State:** _____ **Zip:** _____

Neurologist: _____ **Phone Number:** _____

Address: _____ **City**: _____ **State:** _____ **Zip:** _____

Medical History:

Family History of ALS: *(check one)* o Yes o No o Not Available

Lived in Jefferson County, MO since what date: _____ (year)

Residences before age 16:_____

_____

_____

_____

_____

DRG Code: *(check one)*

o ALS (335.20) o Other_____

Zip Code: *(check one)*

o 63010 o 63012 o 63016 o 63019 o 63020 o 63023 o 63025 o 63026 o 63028 o 63030 o 63041

o 63047 o 63048 o 63049 o 63050 o 63051 o 63052 o 63053 o 63057 o 63065 o 63066 o

63069
o 63070 o 63083 o 63087 o Other _____

Clinical record address documented or other evidence patient resided within Jefferson County, MO at least 2 weeks between
January 1, 1998 – December 31, 2000: *(check one)* o Yes o No o Not Available

Dates resided in Missouri at least 2 weeks between January 1, 1998 – December 31, 2000: ____/____/_____
____/____/_____

Dates of most recent medical records with definitive clinical information:____/____/_____ ____/____/_____
____/____/_____

Motor Neuron (MN) Disease Muscle Groups:	**Bulbar**		**Cervical**		**Thoracic**		**Lumbosacral**	
Atrophy	o Yes	o No	o Yes	o No	o Yes	o No	o Yes	o No
Weakness	o Yes	o No	o Yes	o No	o Yes	o No	o Yes	o No
Fasciculations	o Yes	o No	o Yes	o No	o Yes	o No	o Yes	o No
Other Lower MN	o Yes	o No	o Yes	o No	o Yes	o No	o Yes	o No
Spasticity	o Yes	o No	o Yes	o No	o Yes	o No	o Yes	o No
Other Upper MN	o Yes	o No	o Yes	o No	o Yes	o No	o Yes	o No

Increased Reflexes? o Yes o No **Babinski Signs?** o Present o Absent
Hoffman Sign? o Present o Absent **Jaw Jerk?** o Present o Absent

Nerve conduction study with repetitive stimulation: Date: ____/____/_____
Results:_____

Electromyography: Date: ____/____/_____
Results:_____

Sensory deficits: *(check one)* o Yes o No o Not Available
Explain:_____

MRI performed: *(check all that apply)* o Head o Neck o Spine MRI
Results:_____

Laboratory Information (Already Obtained):

Urine:
24 hours urine for heavy metals: o Yes o No o Not Available **Reults:** o Negative o Normal o Other
_____

Heavy Metals:
Serum Lead: o Normal o Not Available Serum aluminum: o Normal o Not Available Other: o Normal o Not Available

CSF Analysis:
o Normal o Abnormal o Not Done

Other laboratory work performed: *(check all that apply)*
o Lyme Antibody o Immunoprotein Electrophoresis o THS
o Folate o Serum Calcium o B12

Abnormal Lab Results:
_____
_____
_____

Pharmacy Data:

Riluzole prescribed: *(check one)* o Yes o No o Not Available

Abstractor Information:

Abstractor Name: _____ **Date:** _____/_____/_____

Abstractor Signature: _____

Comments:

_____
_

_____
_____

_____
_____

Remainder of Form To Be Completed by Consulting Investigation Neurologist:

ALS Diagnosis: *(check one)*
o Definite ALS o Probable ALS o Possible ALS o Undocumented Definite/Probable ALS
o Undocumented Possible ALS o Definitely Not ALS by Epidemiological Criteria

ICD Code(s): _____

Date of Onset: _____/_____/_____ **Date of Diagnosis:** _____/_____/_____

Supporting Comments:

_____
_____

_____
_____

_____
_____

_____
_____

_____
_____

Multiple Sclerosis Abstraction Form

Appendix D

Patient Information:

Medical Record #: _____ **Case #:** _____ **Social Security #:** _____

Name: _____ _____ _____
Last First MI Maiden

Home Address: _____ **City**: _____

State: _____ **Zip:** _____ **County:** _____ **Date of Birth**: ____/____/_____

DD MM YYYY

Race/Ethnicity: *(check one)* o African American o Asian o Pacific Islander **Sex:** *(check one)* o Female o Male o Hispanic/Latino o White o American Indian o Other_____

Occupation When First Diagnosed:_____

Case Referred From: *(check all that apply)*

o Neurologist o Primary Care Physician o CHIIME/DHSS Database Passive Surveillance
o Hospital DRG Active Surveillance o Pharmacy Active Surveillance o Patient Self Referral
o Community Advocacy Group o Home Nursing Care Agency

Physician Information:

Initial Diagnosing Physician: _____ **Phone Number:** _____

Address: _____ **City**: _____ **State:** _____ **Zip:** _____

Neurologist: _____ **Phone Number:** _____

Address: _____ **City**: _____ **State:** _____ **Zip:** _____

Medical History:

Family History of MS: *(check one)* o Yes o No o Not Available

Lived in Jefferson County, MO since what date: _____ (year)

Residences before age 16:_____

_____

_____

_____

_____

DRG Code: *(check one)*

o MS (340) o Other Demyelinating Diseases (341,341.8-9) o Transverse myelitis (323.9)
o Optic Neuritis (377.3) o Other_____

Zip Code: *(check one)*

o 63010 o 63012 o 63016 o 63019 o 63020 o 63023 o 63025 o 63026 o 63028 o 63030 o 63041
o 63047 o 63048 o 63049 o 63050 o 63051 o 63052 o 63053 o 63057 o 63065 o 63066 o 63069
o 63070 o 63083 o 63087 o Other _____

Clinical record address documented or other evidence patient resided within Jefferson County, MO at least 2 weeks between
January 1, 1998 – December 31, 2000: *(check one)* o Yes o No o Not Available

Age of Onset 15-59 years: *(check one)* o Yes o No o Not Available

Other diagnoses co-existing: (*list)*

_____

_____

_____

Other conditions considered:

(list)_____

_____

_____

Evidence of exacerbations: *(check one)* o Yes o No o Not Available **(>1 day)** ____/____/_____

Evidence of remissions: *(check one)* o Yes o No o Not Available **(28 day interval)** ____/____/_____

Number of attacks: *(check one)* o 0 o 1 o 2 o 3 o 4 o >4 **First Attack** ____/____/_____ **Second Attack** ____/____/_____

Number of clinically diagnosed lesions: *(check one)* o 0 o 1 o 2 o >2 o Not Available

Date of first symptom: ____/____/_____

Symptoms:	**Date of Onset**	**Remission Date**	**Relapse Date**	**Bilateral?**
Weakness of limbs	____/____/_____	____/____/_____	____/____/_____	o Yes o No o Not Available
Sensory loss	____/____/_____	____/____/_____	____/____/_____	o Yes o No o Not Available
Paresthesias	____/____/_____	____/____/_____	____/____/_____	o Yes o No o Not Available
Optic neuritis	____/____/_____	____/____/_____	____/____/_____	o Yes o No o Not Available
Diplopia	____/____/_____	____/____/_____	____/____/_____	o Yes o No o Not Available
Sensory symptoms	____/____/_____	____/____/_____	____/____/_____	o Yes o No o Not Available
Ataxia	____/____/_____	____/____/_____	____/____/_____	o Yes o No o Not Available
Vertigo	____/____/_____	____/____/_____	____/____/_____	o Yes o No o Not Available
Paroxysmal attacks	____/____/_____	____/____/_____	____/____/_____	o Yes o No o Not Available
Bladder dysfunction	____/____/_____	____/____/_____	____/____/_____	o Yes o No o Not Available
Lhermitte	____/____/_____	____/____/_____	____/____/_____	o Yes o No o Not Available
Other_____	____/____/_____	____/____/_____	____/____/_____	o Yes o No o Not Available

Comments:_____

_____

_____

Abnormal physical (neurological examination) ever documented: o Yes o No o Not Available

Increased Reflexes? o Yes o No **Babinski Signs?** o Present o Absent
Hoffman Sign? o Present o Absent **Jaw Jerk?** o Present o Absent

Kurtzke Funtional Status (FS) Scores: A_____ B_____ C_____ D_____ E_____ F_____ G_____ **Date**: _____/_____/_____

Score of 0-6 0-5 0-5 0-6 0-6 0-6 0-5

Physical Exam:	**Date of Onset**	**Remission Date**	**Relapse Date**	**Bilateral?**
Pyramidal Functions:				
Monoparesis or any limb motor abnormality	____/____/_____	____/____/_____	____/____/_____	o Yes o No o Not Available
Hemiparesis	____/____/_____	____/____/_____	____/____/_____	o Yes o No o Not Available
Paraparesis	____/____/_____	____/____/_____	____/____/_____	o Yes o No o Not Available
Quadriplegia	____/____/_____	____/____/_____	____/____/_____	o Yes o No o Not Available

o No limb weakness or spasticity

Cerebellar Functions:

Any ataxia	____/____/_____	____/____/_____	____/____/_____	o Yes	o No
o Not Available					
Truncal ataxia	____/____/_____	____/____/_____	____/____/_____	o Yes	o No
o Not Available					
Limb ataxia	____/____/_____	____/____/_____	____/____/_____	o Yes	o No
o Not Available					
Non-ambulatory due to uncoordinated movements	____/____/_____	____/____/_____	____/____/_____	o Yes	o No
o Not Available					

o No uncoordinated movements noted

Brainstem Functions:

Nystagmus	____/____/_____	____/____/_____	____/____/_____	o Yes	o No
o Not Available					
Extraocular muscle abnormality/weakness	____/____/_____	____/____/_____	____/____/_____	o Yes	o No
o Not Available					
Dysarthria	____/____/_____	____/____/_____	____/____/_____	o Yes	o No
o Not Available					
Dysphagia or unable to speak	____/____/_____	____/____/_____	____/____/_____	o Yes	o No
o Not Available					
Other cranial nerve abnormality	____/____/_____	____/____/_____	____/____/_____	o Yes	o No
o Not Available					

o No problems with cranial nerves noted

Sensory Functions: (Record most abnormal Spinal Cord Sensory Level in parentheses [C, T, L, S, and number, e.g, T-12])

Abnormal vibratory sensation (__-__)	____/____/_____	____/____/_____	____/____/_____	o Yes	o No
o Not Available					
Abnormal touch/finger writing Proprioception (__-__)	____/____/_____	____/____/_____	____/____/_____	o Yes	o No
o Not Available					
Abnormal pain sensation (__-__)	____/____/_____	____/____/_____	____/____/_____	o Yes	o No
o Not Available					

o No problems with sensation noted

Bowel/Bladder Functions:

Urinary hesitancy/urgency/retention	____/____/_____	____/____/_____	____/____/_____	o Yes	o No
o Not Available					
Bladder catheterization	____/____/_____	____/____/_____	____/____/_____	o Yes	o No
o Not Available					
Incontinence of bowel or bladder	____/____/_____	____/____/_____	____/____/_____	o Yes	o No
o Not Available					
Constipation	____/____/_____	____/____/_____	____/____/_____	o Yes	o No
o Not Available					

o No bladder or bowel problems noted

Visual/Optic Functions:

Scotoma [blind spot(s)]	____/____/_____	____/____/_____	____/____/_____	o Yes	o No
o Not Available					
Abnormal visual acuity (after correction with lenses)	____/____/_____	____/____/_____	____/____/_____	o Yes	o No
o Not Available					

o No problems with corrected visual acuity

Cerebral Functions:

Organic Brain Syndrome	____/____/_____	____/____/_____	____/____/_____	o Yes	o No
o Not Available					

o No organic brain syndrome noted

Comments:_____

_____

_____

Abnormal MRI: o Yes o No o Not Available

MRI Findings/Locations:	Date	White Matter Lesions
Number of lesions (L) >3mm	____/____/_____	o 1 o 2 o 3 o 4 o >4
Number of Lesions >5mm	____/____/_____	o 1 o 2 o 3 o 4 o >4
Number of L adjacent to lateral ventricles	____/____/_____	o 1 o 2 o 3 o 4 o >4
Number of lesions in posterior fosa	____/____/_____	o 1 o 2 o 3 o 4 o >4
Number of lesions in spinal cord	____/____/_____	o 1 o 2 o 3 o 4 o >4

MRI Narrative:

_____

CT Scan Results:

_____

Laboratory Information (Already Obtained):

Abnormal Laboratory Studies (evoked responses or CSF): o Yes o No o Not Available

Evoked Responses:				Date	Comments
Visual ER	o Normal	o Slowed	o Absent	____/____/_____	
Auditory ER	o Normal	o Slowed	o Absent	____/____/_____	
Somatosensory ER	o Normal	o Slowed	o Absent	____/____/_____	
Motor ER	o Normal	o Slowed	o Absent	____/____/_____	

Cerebrospinal Fluid:
Date: ____/____/_____ Obligoclonal bands: o 0 o 1 o 2 o >2 o Not Available
CSF IgG/serum IgG >1: o Yes o No o Not Available Pleocytosis: o Yes o No o Not Available
CSF Total Protein: _____ CSF WBC _____ CSF percent PMN _____%

Urine:
24 hours urine for heavy metals: o Yes o No o Not Available **Results:** o Negative o Normal o Other
_____

Heavy Metals:
Serum Lead: o Normal o Not Available Serum aluminum: o Normal o Not Available Other: o Normal o Not Available

Other laboratory work performed: *(check all that apply)*
o B-12 o Rheumatoid factor o ANA o Anti DNS antibodies
o VDRL o Angiotensin converting enzyme o Lyme titer o Not Available

Abnormal Lab Results:
_____

Pharmacy Data:

Medications prescribed: *(check all that apply)*
o Beta interferons (Avonex or BetaSeron) o Glatiramer acetate (Copaxone) o Mitoxantrone (Novantrone)

Abstractor Information:

Abstractor Name: _____ **Date:** _____/_____/_____

Abstractor Signature: _____

Comments:
_____
_
_____
_____
_____
_____

Remainder of Form To Be Completed by Consulting Investigation Neurologist:

MS Diagnosis: *(check one)*
o Definite MS o Probable MS o Possible MS o Undocumented Definite/Presumptive MS
o Undocumented Possible MS o Definitely Not MS by Epidemiological Criteria

ICD Code(s): _____

Date of Onset: _____/_____/_____ **Date of Diagnosis:** _____/_____/_____

Supporting Comments:

_____
_____

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_____

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_____

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